General

Guideline Title

Radiotherapy with curative intent in patients with early stage, medically inoperable, non-small cell lung cancer.

Bibliographic Source(s)

Falkson CB, Vella E, Yu E, El-Mallah M, Ung YC, Ellis PM, Mackenzie R, Lung Disease Site Group. Radiotherapy with curative intent in patients with early stage, medically inoperable, non-small cell lung cancer. Toronto (ON): Cancer Care Ontario (CCO); 2016 May 4. 59 p. (Program in Evidence-based Care Guideline; no. 7-21). [105 references]

Guideline Status

This is the current release of the guideline.

The Program in Evidence-based Care (PEBC) Guideline over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendation 1

Stereotactic body radiation therapy (SBRT) with curative intent is an option that should be considered for patients with early stage, node-negative, medically inoperable non-small cell lung cancer (NSCLC).

Note: Stereotactic body radiation therapy and stereotactic ablative radiation therapy are considered synonymous for the purposes of this guideline and are referred to as SBRT.

Recommendation 2

Recommended fractionation schemes for SBRT should have a $BED_{10(LQ)}$* of ≥100.

*BED, biological effective dose; LQ, linear quadratic.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Early stage, medically inoperable, non-small cell lung cancer (NSCLC)

Guideline Category

Treatment

Clinical Specialty

Oncology

Pulmonary Medicine

Radiation Oncology

Thoracic Surgery

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

Guideline Objective(s)

To investigate the effectiveness of radiotherapy with curative intent in patients with early stage non-small cell lung cancer (NSCLC) who are medically inoperable

Target Population

Adult patients with potentially curable, early stage (Stage I or II) non-small cell lung cancer (NSCLC) (without nodal involvement or metastases), and who are deemed medically inoperable or refuse surgery

Interventions and Practices Considered

1. Stereotactic body radiation therapy (SBRT) and stereotactic ablative radiation therapy with curative intent
2. Dose/fractionation schemes for SBRT

Major Outcomes Considered

- 2-, 3-, and 5-year survival rate
- Overall survival
- Disease-free survival (DFS)
- Local and non-local relapse-free survival
- Regional relapse-free survival (RRFS)
- Cause-specific survival (CSS)
- Distant relapse-free survival (DRFS)
- Local control/recurrence
- Toxicity (e.g., radiation pneumonitis, chest wall toxicity)
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework, or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

1. Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), National Guideline Clearinghouse (NGC), and Inventory of Cancer Guidelines
2. Guideline developer Web sites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network.

Only guidelines published in English after 2008 were considered. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. This search yielded five practice guidelines. The Working Group decided that proceeding with a new systematic review that included the latest research was warranted due to the relatively frequent release of information and a need to focus on treatment. Existing guidelines were either not up to date, or addressed a broader scope than was required by this treatment guideline.

Methods

The Program in Evidence-Based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. This evidentiary base was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews were identified that addressed the research questions, then those systematic reviews were included in the evidentiary base.
2. Systematic review of the primary literature: This search would focus on those areas not covered by existing systematic reviews.

Search for Existing Systematic Reviews

A search for systematic reviews was carried out on the topic of radiation treatment with curative intent in patients with medically inoperable non-small cell lung cancer (NSCLC). This search was conducted within the Cochrane library, MEDLINE, and EMBASE databases from January

1985 to July 2015. Systematic reviews were included if they addressed either of the research questions and reported on the sources searched. *A priori*, the Working Group decided that the main comparison would be stereotactic body radiation therapy (SBRT) against other forms of radiotherapy; therefore, the systematic reviews had to focus on SBRT and either compare it with other radiotherapies or examine the most appropriate dose or fractionation schemes for SBRT. Results were limited to articles published in English. Identified systematic reviews were assessed using the assessment of multiple systematic reviews (AMSTAR) tool.

Search for Primary Literature

Literature Search Strategy

The literature was searched using MEDLINE (1985 through July 16, 2015), EMBASE (1985 through July 16, 2015), the Cochrane Database of Systematic Reviews (OVID CDSR: March 2014), the Cochrane Central Register of Controlled Trials (OVID CCTR: April 2014), and the Database of Abstracts of Reviews of Effects (OVID DARE: 1st quarter 2014). In addition, the proceedings of the meetings of the American Society of Clinical Oncology (ASCO: 2007 to 2014), the American Society of Therapeutic Radiology and Oncology (ASTRO: 2007 to 2013), and the European Society for Radiotherapy and Oncology (ESTRO: 2007 to 2014) were searched for relevant abstracts. Reference lists of studies deemed eligible for inclusion were scanned for additional citations.

The literature search of the electronic databases combined disease-specific terms (lung carcinoma, non-small cell lung cancer, NSCLC, etc.) along with disease stage-specific terms (early stage, medically inoperable) and treatment-specific terms (radiation, stereotactic, hypofractionation) for all study designs (see Appendix 2 of the original guideline document).

Study Selection Criteria and Process

Inclusion Criteria

Articles were eligible for inclusion in this systematic review if they met the following criteria:

1. Studies included full reports or abstracts of randomized controlled trials (RCTs) or other comparative trials with more than 50 participants. Interventions considered were stereotactic radiation treatment with curative intent compared with observation or other types of radiotherapy for early stage, medically inoperable, NSCLC. Comparisons between radiation dosing or fractionation schedules for SBRT were included.
2. Studies included patients with a tumour size less than 5 cm (i.e., T1 or T2a), node-negative (i.e., N0), medically inoperable NSCLC.
3. Studies reported data on survival, local control, adverse events, or quality of life.

Exclusion Criteria

1. Interventions were combined with limited surgery or chemotherapy.
2. Radiation therapy was not used with curative intent or as second-line treatment.

A review of the titles and abstracts that resulted from the search was conducted by one reviewer. For those items that warranted full-text review, one reviewer reviewed each item in collaboration with a second reviewer if uncertainty existed.

Refer to the "Results" section of the original guideline document for information on studies retrieved through the literature searches.

Number of Source Documents

Existing Guidelines: The search yielded five practice guidelines. Existing guidelines were either not up to date, or addressed a broader scope than was required by this treatment guideline.

Existing Systematic Reviews: Four systematic reviews were included.

Primary Literature: 52 studies met the pre-defined eligibility criteria for this systematic review.

See also the PRISMA flow diagram in Appendix 3 of the original guideline document.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

All eligible studies underwent data extraction independently by a research methodologist, with all extracted data and information subsequently audited by an independent auditor. Ratios, including hazard ratios (HR), were expressed such that a ratio <1.0 indicated a survival benefit favouring non-stereotactic radiation therapy; conversely, a survival benefit that favoured patients treated with stereotactic radiation therapy was expressed by a HR >1.0.

An assessment of study quality was performed for all the included primary literature by one methodologist. Cohort studies were assessed using A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI).

Synthesizing the Evidence

A meta-analysis was not planned because of the variability in dose and fractionation schedules and the inconsistent stereotactic body radiation therapy (SBRT) procedures due to evolving technologies in the field.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Developers

This guideline was developed by the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer (NSCLC) Guideline Development Group (GDG) (see Appendix 1 in the original guideline document), which was convened at the request of the Radiation treatment program along with the Lung Disease Site Group.

The project was led by a small Working Group of the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in radiation oncology, medical oncology, and health research methodology. Other members of the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.

Guideline Development Methods

The Program in Evidence-Based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. This process includes a systematic review, interpretation of the evidence by the Working Group who then draft recommendations based on the evidence and expert consensus, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines Research and Evaluation (AGREE) II framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the PEBC Document Assessment and Review Protocol (see the "Availability of Companion Documents" field). PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Research Questions

The Working Group derived the following research questions:

1. What is the effectiveness of radiotherapy with curative intent in patients with early stage NSCLC who are unable to undergo surgery?
2. What are the most effective dose/fractionation schedules for curative intent radiotherapy?

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the Guideline Development Groups (GDG) Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

See Section 5 in the original guideline document for further discussion of the internal and external guideline review process and results.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by systematic reviews and nonrandomized, prospective or retrospective cohort studies.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Although the evidence was from retrospective cohort studies, the consistency of the results led the Working Group to believe that the potential benefits in overall survival and local control with stereotactic body radiation therapy (SBRT) compared with observation and other radiotherapies, especially older conventional therapy treatments, outweighed the potential harms associated with SBRT for medically inoperable patients with early stage non-small cell lung cancer (NSCLC). Therefore, they considered SBRT to be a recommended treatment option for this patient population.
- Although there was variability in results using a biological effective dose (BED) cut-off of approximately 100, the largest studies suggested that a BED close to 100 was associated with overall survival and local control. The Working Group believed that recommending a minimal BED threshold would maximize the beneficial outcomes associated with SBRT without increasing harm.

Potential Harms

Toxicities of radiation therapy, such as pneumonitis, bleeding, esophagitis, dyspnea, coughing, rib fracture, chest wall pain, skin toxicity, and treatment-related death

Qualifying Statements

Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nevertheless, any person seeking to apply or consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.
- See the original guideline document for qualifying statements related to each recommendation.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Considerations

The Working Group considered these recommendations to be the current standard of care and thus would be feasible to implement. They believe the outcomes valued in this guideline would align with patient values and that patients would view these recommendations as acceptable.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report

Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 May 4

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer Working Group

Lung Disease Site Group Expert Panel

Composition of Group That Authored the Guideline

Authors: C. B. Falkson, E. Vella, E. Yu, M. El-Mallah, Y. C. Ung, P. M. Ellis, R. Mackenzie, Lung Disease Site Group

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-Based Care (PEBC) Conflict of Interest (COI) Policy, the Members of the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer Working Group, Expert Panel, Report Approval Panel and Target Peer Reviewers were asked to disclose potential conflicts of interest.

See Appendix 1 in the original guideline document for information on authors' affiliations and conflict of interest declarations.

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This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site.

Availability of Companion Documents

The following are available:

- Radiotherapy with curative intent in patients with early stage, medically inoperable, non-small cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2016 May 4. 4 p. Available from the Cancer Care Ontario (CCO) Web site.
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the CCO Web site.
- Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site.
- Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the CCO Web site.

Patient Resources

None available

NGC Status

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